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File: PGPB

Jan 22, 2004

DOCUMENT-IDENTIFIER: US 20040013717 A1
TITLE: PEG-lipid containing formulations

Detail Description Paragraph:

Critical Micelle Concentration (CMC) of PEG-Phospholipid Micelle With and Without
QLT 0069

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L5: Entry 3 of 8

File: PGPB

Aug 22, 2002

DOCUMENT-IDENTIFIER: US 20020115609 A1

TITLE: Materials and methods for making improved micelle compositions

Summary of Invention Paragraph:

[0027] Different investigators reported that only 5% PEG-PE could give an optimized steric barrier effect on the vesicles (Klibanov et al., Biochim. Biophys. Acta 1062:142-148 (1991); Woodle et al., Biochim. Biophys. Acta 1105:193-200 (1992); McIntosh et al., Stealth Liposomes, D. Lasic and F. Martin (Eds.), CRC Press, Boca Raton, Fla., pp. 63-71 (1995)). A maximal limit of 10 mol % PEG was very recently proposed to obtain adequate results from in vitro studies, because of the spontaneous formation of micelles of PEG-PE at higher concentrations (Bedu-Addo et al., Pharm. Res. 13:718-724 (1996)).

Summary of Invention Paragraph:

[0029] Of interest to the present invention is work relating to molecular aggregates called "micelles" which are defined as colloidal aggregates spontaneously formed by amphiphilic compounds in water above a critical solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT). The molecules constituting the micelles are in rapid dynamic equilibrium with the unassociated molecules. The increase in the concentration above the CMC usually leads to an increase in the number of micelles without any change in micellar size; however, in certain cases with phospholipid mixed micelles, the spherical micelles enlarge into rod-shaped micelles (Carey et al., Arch. Inter Med. 130:506-527 (1972); Hjelm, Jr. et al., J. Phys. Chem. 96 (21):8653-8661 (1992)). The CMC is strongly temperature dependent, and at a given concentration the monomer to micelle transition occurs gradually over a broad temperature range (Almgren et al., Colloid Polym. Sci. 273:2-15 (1995)). An increase in the temperature leads to an increase in the number of aggregates, while the hydrodynamic radius remains constant (Nivaggioli et al., Langmuir. 11 (3):730-737 (1995); Alexandridis et al., Langmuir. 11: 1468-1476 (1995)). In general the increase in temperature leads to an increase in hydrophobic interactions and the water dielectric constant is reduced augmenting the ionic repulsion forces. There are many ways to determine the CMC of an amphiphilic compound (surface tension measurements, solubilization of water insoluble dye, or a fluorescent probe, conductivity measurements, light scattering, and the like). According to a preferred method, surface tension measurements may be used to determine the CMC of PEG-DSPE micelles at room temperature.

Summary of Invention Paragraph:

[0041] The present invention provides improved methods of preparing biologically active micelle products comprising one or more biologically active amphipathic compounds in association with a micelle. As used herein, compounds embrace peptides, proteins, enzymes in general, as well as fragments, analogs, and modulators thereof. With respect to proteins, the invention contemplates use of both L and D forms. Where compounds of the invention exist in both cis and trans conformations, the invention comprehends use of either form alone or a combination of both forms. The micellar formulations of the invention deliver and enhance bioactivity of the biologically active peptides in a manner which provides improvements in the efficacy and duration of the biological effects of the associated peptides. Increased efficacy and duration of the biological effect is

believed to result, at least in part, from interaction of the compound with the micelle in such a manner that the compound attains, and is maintained in, an active or more active conformation than the compound in an aqueous environment. The invention thus overcomes the problems associated with previous liposomal formulations, such as, but not limited to, uptake by the reticuloendothelial system, degradation of the compound, or delivery of the compound in an inactive conformation. According to one aspect of the present invention, polyethylene-glycol (PEG) is covalently conjugated to DSPE and used to form polymeric micelles which are then passively loaded with VIP. The PEG-DSPE forms micelles with a hydrophobic core consisting of distearoyl phosphatidylethanolamine (DSPE) fatty acid chains which is surrounded by a hydrophilic "shell" formed by the PEG polymer.

Summary of Invention Paragraph:

[0051] Methods of the invention for producing sterically stabilized crystalline products are amenable to the use of any compound that is insoluble in an aqueous solution. Preferred insoluble compounds include, but are not limited to, progesterone, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, amphotericin B, betulinic acid, camptothecin, diazepam, nystatin, propofol, cyclosporin A, doxorubicin, and Taxol.RTM., and tetramethyl NDGA. In methods of the invention for producing sterically stabilized crystalline product further comprising one or more targeting compounds, any targeting compound that assumes or maintains a biologically active conformation when in association with the sterically stabilized crystalline product can be used. In a preferred embodiment, any of the amphipathic compounds as described above are utilized. In a most preferred embodiment, the targeting compound is VIP or other member of the VIP/GRF family or proteins.

Summary of Invention Paragraph:

[0056] In one embodiment, method of treating a pathology selected from the group consisting of autism, multiple sclerosis, enuresis, Parkinson's disease, amyotrophic lateral sclerosis, and AIDS-associated dementias according to the invention include micelle compositions or crystalline compounds wherein the water soluble polymer is polyethylene glycol (PEG). In another embodiment, method of the invention include use of micelles having an average diameter of less than about 25 nm. In still another embodiment, methods of the invention include micelle compositions or crystalline compounds wherein the combination of lipids consists of distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE).

Summary of Invention Paragraph:

[0060] In one embodiment, medicaments of the invention include micelle compositions or crystalline compounds wherein the water soluble polymer is polyethylene glycol (PEG). In another embodiment, medicaments of the invention include use of micelles having an average diameter of less than about 25 nm. In still another embodiment, medicaments of the invention include micelle compositions or crystalline compounds wherein the combination of lipids consists of distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE).

Brief Description of Drawings Paragraph:

[0061] FIG. 1 depicts surface tension measurements of a PEG-DSPE aqueous solution to determine the critical micelle concentration (CMC) at room temperature;

Detail Description Paragraph:

[0070] In methods of the invention to prepare sterically stabilized crystalline products, any compound that is insoluble in an aqueous solution can be incorporated into crystalline product. In methods of the invention, the insoluble compounds associate in the hydrophobic core of the associated lipids to the extent that the insoluble compound crystallizes. While the invention contemplates the use of any insoluble compound to produce the crystalline products, preferred compounds are normally insoluble anti-cancer agents, antifungal agents, sedatives, and steroidal compounds. Most preferably, the insoluble compounds are selected from the group

consisting of Taxol.RTM., betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, and progesterone.

Detail Description Paragraph:

[0071] Micelles according to the invention may be produced from combinations of lipid materials well known and routinely utilized in the art to produce micelles and including at least one lipid component covalently bonded to a water-soluble polymer. Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. The lipid materials may be selected by those of skill in the art in order that the circulation time of the micelles be balanced with the drug release rate. To make full use of the power of these micelles in drug delivery, a key challenge is to prevent the leakage of the drug from the micelle to a level significantly less than the plasma distribution rate. However, this point is probably the fundamental basis of SSL and SSM, since their delivery, which is difficult to control, corresponds to the bioavailability of the encapsulated agent. SSM being more dynamic than liposomes may show superiority to SSL with respect to drug release. Polymers of the invention may thus include any compounds known and routinely utilized in the art of sterically stabilized liposome (SSL) technology and technologies which are useful for increasing circulatory half-life for proteins, including for example polyvinyl alcohol, polylactic acid, polyglycolic acid, polyvinylpyrrolidone, polyacrylamide, polyglycerol, polyaxozlines, or synthetic lipids with polymeric headgroups. The most preferred polymer of the invention is PEG at a molecular weight between 1000 and 5000. Preferred lipids for producing micelles according to the invention include distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE) alone or in further combination with phosphatidylcholine (PC), and phosphatidylglycerol (PG) in further combination with cholesterol (Chol) and/or calmodulin.

Detail Description Paragraph:

[0086] According to this example, VIP was incorporated into sterically stabilized micelles according to the following procedure. In order to determine the concentration of PEG-DSPE needed to prepare micelles, surface tension studies of PEG-DSPE aqueous solutions were performed. The critical micellar concentration was found to be 0.5 to 1.0 μM , thus 1.0 μM of PEG-DSPE was used to ensure formation of micelles (FIG. 1). PEG-DSPE lipid (1 $\mu\text{mol/ml}$) was dissolved in chloroform and mixed in a round bottom flask. The organic solvent was evaporated using a rotoevaporater at a bath water temperature of 45.degree. C. (Labconco, Kansas City, Mo.). Complete dryness was achieved by desiccation under vacuum overnight. The dry lipid film was hydrated with saline (0.15 N, pH 6.8) or HEPES buffer (10 mM, pH 7.4). The solution was incubated with human VIP (13 $\mu\text{g/ml}$) for 30 min before use in circular dichroism. Human VIP (0.1 nmol/ml) was added to the phospholipid micelle suspension and incubated for 2 hours at room temperature before use in cheek pouch studies.

Detail Description Paragraph:

[0092] According to the example, CD was used to determine the conformation of VIP in saline, Hepes buffer and phospholipid micelles at room temperature and at 37.degree. C. The CD spectra analysis was performed after 13 μg of human VIP incubated with 1 ml PEG-DSPE (1 μmol) micelles for 30 min at room temperature as determined by preliminary studies. A bandwidth of 1.0 nm and a step resolution of 0.5 nm were used to collect an average of 9 accumulations/sample at near UV range (200-260 nm). The temperature was maintained during spectral analysis by a circulating water bath attached to a jacket surrounding the fused quartz CD cell. The evaluation of VIP molecule conformation in SSM by using circular dichroism was successful because the distortion caused by spherical particles was eliminate due to the small size and univesicular structure of the SSM. The dynamic nature of the micelles also enhanced the VIP interactions with phospholipids. The phospholipid micelles were ideal in our study of VIP conformation since it provided a

hydrophobic core similar to the phospholipid bilayer of the SSL. Moreover, both the negative charge, and the hydrophilic layer provided by the PEG mimic the conditions of our SSL and make it possible to infer the VIP conformational results.

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File: USPT

Apr 17, 2001

DOCUMENT-IDENTIFIER: US 6217886 B1

TITLE: Materials and methods for making improved micelle compositions

Brief Summary Text (27):

Different investigators reported that only 5% PEG-PE could give an optimized steric barrier effect on the vesicles (Klibanov et al., Biochim. Biophys. Acta 1062:142-148 (1991); Woodle et al., Biochim. Biophys. Acta 1105:193-200 (1992); McIntosh et al., Stealth Liposomes, D. Lasic and F. Martin (Eds.), CRC Press, Boca Raton, Fla., pp. 63-71 (1995)). A maximal limit of 10 mol % PEG was very recently proposed to obtain adequate results from in vitro studies, because of the spontaneous formation of micelles of PEG-PE at higher concentrations (Bedu-Addo et al., Pharm. Res. 13:718-724 (1996)).

Brief Summary Text (29):

Of interest to the present invention is work relating to molecular aggregates called "micelles" which are defined as colloidal aggregates spontaneously formed by amphiphilic compounds in water above a critical solute concentration, the critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT). The molecules constituting the micelles are in rapid dynamic equilibrium with the unassociated molecules. The increase in the concentration above the CMC usually leads to an increase in the number of micelles without any change in micellar size; however, in certain cases with phospholipid mixed micelles, the spherical micelles enlarge into rod-shaped micelles (Carey et al., Arch. Inter Med. 130:506-527 (1972); Hjelm, Jr. et al., J. Phys. Chem. 96 (21):8653-8661 (1992)). The CMC is strongly temperature dependent, and at a given concentration the monomer to micelle transition occurs gradually over a broad temperature range (Almgren et al., Colloid Polym. Sci. 273:2-15 (1995)). An increase in the temperature leads to an increase in the number of aggregates, while the hydrodynamic radius remains constant (Nivaggioli et al., Langmuir. 11 (3):730-737 (1995); Alexandridis et al., Langmuir. 11: 1468-1476 (1995)). In general the increase in temperature leads to an increase in hydrophobic interactions and the water dielectric constant is reduced augmenting the ionic repulsion forces. There are many ways to determine the CMC of an amphiphilic compound (surface tension measurements, solubilization of water insoluble dye, or a fluorescent probe, conductivity measurements, light scattering, and the like). According to a preferred method, surface tension measurements may be used to determine the CMC of PEG-DSPE micelles at room temperature.

Brief Summary Text (42):

The present invention provides improved methods of preparing biologically active micelle products comprising one or more biologically active amphipathic compounds in association with a micelle. As used herein, compounds embrace peptides, proteins, enzymes in general, as well as fragments, analogs, and modulators thereof. With respect to proteins, the invention contemplates use of both L and D forms. Where compounds of the invention exist in both cis and trans conformations, the invention comprehends use of either form alone or a combination of both forms. The micellar formulations of the invention deliver and enhance bioactivity of the biologically active peptides in a manner which provides improvements in the efficacy and duration of the biological effects of the associated peptides. Increased efficacy and duration of the biological effect is believed to result, at

least in part, from interaction of the compound with the micelle in such a manner that the compound attains, and is maintained in, an active or more active conformation than the compound in an aqueous environment. The invention thus overcomes the problems associated with previous liposomal formulations, such as, but not limited to, uptake by the reticuloendothelial system, degradation of the compound, or delivery of the compound in an inactive conformation. According to one aspect of the present invention, polyethylene-glycol (PEG) is covalently conjugated to DSPE and used to form polymeric micelles which are then passively loaded with VIP. The PEG-DSPE forms micelles with a hydrophobic core consisting of distearoyl phosphatidylethanolamine (DSPE) fatty acid chains which is surrounded by a hydrophilic "shell" formed by the PEG polymer.

Brief Summary Text (52):

Methods of the invention for producing sterically stabilized crystalline products are amenable to the use of any compound that is insoluble in an aqueous solution. Preferred insoluble compounds include, but are not limited to, progesterone, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, amphotericin B, betulinic acid, camptothecin, diazepam, nystatin, propofol, cyclosporin A, doxorubicin, and Taxol.RTM.. In methods of the invention for producing sterically stabilized crystalline product further comprising one or more targeting compounds, any targeting compound that assumes or maintains a biologically active conformation when in association with the sterically stabilized crystalline product can be used. In a preferred embodiment, any of the amphipathic compounds as described above are utilized. In a most preferred embodiment, the targeting compound is VIP or other member of the VIP/GRF family or proteins.

Drawing Description Text (2):

FIG. 1 depicts surface tension measurements of a PEG-DSPE aqueous solution to determine the critical micelle concentration (CMC) at room temperature;

Detailed Description Text (3):

In methods of the invention to prepare sterically stabilized crystalline products, any compound that is insoluble in an aqueous solution can be incorporated into to crystalline product. In methods of the invention, the insoluble compounds associate in the hydrophobic core of the associated lipids to the extent that the insoluble compound crystallizes. While the invention contemplates the use of any insoluble compound to produce the crystalline products, preferred compounds are normally insoluble anti-cancer agents, antifungal agents, sedatives, and steroidal compounds. Most preferably, the insoluble compounds are selected from the group consisting of Taxol.RTM., betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, testosterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, and progesterone.

Detailed Description Text (4):

Micelles according to the invention may be produced from combinations of lipid materials well known and routinely utilized in the art to produce micelles and including at least one lipid component covalently bonded to a water-soluble polymer. Lipids may include relatively rigid varieties, such as sphingomyelin, or fluid types, such as phospholipids having unsaturated acyl chains. The lipid materials may be selected by those of skill in the art in order that the circulation time of the micelles be balanced with the drug release rate. To make full use of the power of these micelles in drug delivery, a key challenge is to prevent the leakage of the drug from the micelle to a level significantly less than the plasma distribution rate. However, this point is probably the fundamental basis of SSL and SSM, since their delivery, which is difficult to control, corresponds to the bioavailability of the encapsulated agent. SSM being more dynamic than liposomes may show superiority to SSL with respect to drug release. Polymers of the invention may thus include any compounds known and routinely utilized in the art of sterically stabilized liposome (SSL) technology and technologies which are useful for increasing circulatory half-life for proteins, including for example polyvinyl

alcohol, polylactic acid, polyglycolic acid, polyvinylpyrrolidone, polyacrylamide, polyglycerol, polyaxozlines, or synthetic lipids with polymeric headgroups. The most preferred polymer of the invention is PEG at a molecular weight between 1000 and 5000. Preferred lipids for producing micelles according to the invention include distearoyl-phosphatidylethanolamine covalently bonded to PEG (PEG-DSPE) alone or in further combination with phosphatidylcholine (PC), and phosphatidylglycerol (PG) in further combination with cholesterol (Chol) and/or calmodulin.

Detailed Description Text (20):

According to this example, VIP was incorporated into sterically stabilized micelles according to the following procedure. In order to determine the concentration of PEG-DSPE needed to prepare micelles, surface tension studies of PEG-DSPE aqueous solutions were performed. The critical micellar concentration was found to be 0.5 to 1.0 μM , thus 1.0 μM of PEG-DSPE was used to ensure formation of micelles (FIG. 1). PEG-DSPE lipid (1 $\mu\text{mol/ml}$) was dissolved in chloroform and mixed in a round bottom flask. The organic solvent was evaporated using a rotoevaporator at a bath water temperature of 45.degree. C. (Labconco, Kansas City, Mo.). Complete dryness was achieved by desiccation under vacuum overnight. The dry lipid film was hydrated with saline (0.15 N, pH 6.8) or HEPES buffer (10 mM, pH 7.4). The solution was incubated with human VIP (13 $\mu\text{g/ml}$) for 30 min before use in circular dichroism. Human VIP (0.1 nmol/ml) was added to the phospholipid micelle suspension and incubated for 2 hours at room temperature before use in cheek pouch studies.

Detailed Description Text (27):

According to the example, CD was used to determine the conformation of VIP in saline, Hepes buffer and phospholipid micelles at room temperature and at 37.degree. C. The CD spectra analysis was performed after 13 μg of human VIP incubated with 1 ml PEG-DSPE (1 μmol) micelles for 30 min at room temperature as determined by preliminary studies. A bandwidth of 1.0 nm and a step resolution of 0.5 nm were used to collect an average of 9 accumulations/sample at near UV range (200-260 nm). The temperature was maintained during spectral analysis by a circulating water bath attached to a jacket surrounding the fused quartz CD cell. The evaluation of VIP molecule conformation in SSM by using circular dichroism was successful because the distortion caused by spherical particles was eliminate due to the small size and univesicular structure of the SSM. The dynamic nature of the micelles also enhanced the VIP interactions with phospholipids. The phospholipid micelles were ideal in our study of VIP conformation since it provided a hydrophobic core similar to the phospholipid bilayer of the SSL. Moreover, both the negative charge, and the hydrophilic layer provided by the PEG mimic the conditions of our SSL and make it possible to infer the VIP conformational results.

CLAIMS:

31. The method of claim 7, wherein the soluble compound is selected from the group consisting of progesterone, estrogen, prednisolone, prednisone, 2,3 mercaptopropanol, testosterone, betulinic acid, doxorubicin, amphotericin B, diazepam, nystatin, propofol, and Taxol.RTM..

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Jan 22, 2004

DOCUMENT-IDENTIFIER: US 20040013717 A1

TITLE: PEG-lipid containing formulations

Summary of Invention Paragraph:

[0013] Further, freeze-dried pharmaceutical formulations comprising a porphyrin photosensitizer, a disaccharide or polysaccharide, and one or more phospholipids (such as EPG and DMPC) have been made. These formulations form liposomes containing an effective amount of porphyrin photosensitizer upon reconstitution with a suitable aqueous vehicle and are described in Desai et al., U.S. Pat. No. 6,074,666, which is incorporated by reference. Methods for the large-scale production of DMPC/EPG liposomes containing a photosensitizer are disclosed in U.S. Pat. No. 5,707,608, which is incorporated by reference as if fully set forth.

Detail Description Paragraph:

[0030] In addition to the micelle and micelle-containing compositions of the invention, the present invention provides methods for formulating said micelles. In one embodiment, such methods involve dissolving the amphipathic molecule, such as PEG.sub.2000-DSPE, and one or more active agent in a suitable solvent, such as dichloromethane, followed by solvent removal to form a thin film. The thin film may be hydrated with an aqueous solvent to form a solution comprising micelles for administration or application or for sterilization by a 0.22 .mu.m filter. The film may also be divided into portions before being individually hydrated. Alternatively, the micelles may be formed by adding a miscible volatile solvent containing a PS and PEG-lipid to an aqueous phase, such that the organic phase is removed (e.g. by heating the mixture), leaving the aqueous micelle-containing PS in solution. Various amounts of active agent may be used within suitable ranges of the (molar) lipid:active agent ratio. Preferred ratios are from about 0.5 to about 10 or about 20. Ratios of about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, and about 9, about 10, up to about 19 may also be used. Preferred ratios for the practice of the invention are from about 2 to about 6 or about 6 to about 10. Additionally within the scope of the invention are the intermediate ratios within the range, such as from about 4.1:1 to 4.9:1, about 5.1:1 to 5.9:1, about 6.1:1 to 6.9:1, about 7.1:1 to 7.9:1, and about 8.1:1 to 8.9:1, are within the scope of the invention.

Detail Description Paragraph:

[0082] In a preferred embodiment of the invention, the micelles can be further stabilized by lyophilization. Micelles of the invention may contain a cryoprotectant for stabilization during lyophilization. Alternatively, the physical structures of the micelles can be preserved by the presence of sufficient water after lyophilization. This is may be accomplished by appropriate control of the degree of lyophilization.

Detail Description Paragraph:

[0083] Any cryoprotective agent known to be useful in the art of preparing freeze-dried formulations, such as di- or polysaccharides or other bulking agents such as lysine, may be used in the claimed invention. Further, isotonic agents typically added to maintain isomolarity with body fluids may be used. In preferred embodiments, a di-saccharide or polysaccharide is used and functions both as a cryoprotective agent and as an isotonic agent. In an especially preferred

embodiment, the disaccharide or polysaccharide is selected from among the group consisting of lactose, trehalose, maltose, maltotriose, palatinose, lactulose or sucrose, with lactose or trehalose being preferred. Effective sugars such as trehalose and lactose are capable of hydrogen bonding to the phospholipidhead group in place of water.

Detail Description Paragraph:

[0086] Freeze-Drying

Detail Description Paragraph:

[0087] Once formulated, the micelles of the invention may be freeze-dried or lyophilized for long-term storage if desired. For example, BPD-MA, a preferred hydro-monobenzoporphyrin photosensitizer, has maintained its potency in a cryodesiccated composition for a period of at least nine months at room temperature, and a shelf life of at least two years has been projected. If the composition is freeze-dried, it may be packed in vials for subsequent reconstitution with a suitable aqueous solution, such as sterile water or sterile water containing a saccharide and/or other suitable excipients, just prior to use. For example, reconstitution may be by simply adding water for injection just prior to administration.

Detail Description Paragraph:

[0088] Various lyophilization techniques are known in the art. For example, micelle-containing vials of the invention may be first frozen to -45.degree. C. and then held there for a period of up to about 90 minutes. This may be followed by a high vacuum primary drying cycle wherein the temperature is increased slowly to up to about 10.degree. C. for a period usually on the order of about 50 hours. This may be followed by a 20.degree. C. secondary drying cycle of up to about 24 hours. Once the lyophilizer pressure stabilizes at about 55-65 mTorr (73-87 microbar), the cycle is terminated. Thereafter, the vials may be sealed after overlaying with nitrogen gas. A general rule for freeze-drying is that a solid, brittle, non-collapsed, and homogenous cake is preferred for successful re-hydration.

Detail Description Paragraph:

[0089] Additionally, the use of lyophilization may prevent hydrolysis of hydrophobic agents susceptible to such reactions. For example, the photosensitizer BPD-MA may be hydrolyzed to BPD-DA.

Detail Description Paragraph:

[0107] Alternatively, the solution may be aliquoted followed by lyophilization. Prior to hydration, the solid material may be warmed to room temperature while protected from light.

Detail Description Paragraph:

[0113] Table 3 shows the results before and after filtration with verteporfin-containing micelles after hydration in 20 mM phosphate buffer at pH 8.5 (where "5DW" refers to 5% dextrose water). The micelles were fully solubilized, as demonstrated by their filterability through 0.22 micron filters.

Detail Description Paragraph:

[0116] These results show that both the A-ring and B-ring benzoporphyrin derivatives can be readily entrapped in PEG.sub.2000-DSPE micelles at drug concentrations as high as 1-2 mg/ml. The incorporation efficiency of the B-ring benzoporphyrin derivative, QLT 0069 depended on both the lipid:drug molar ratio and the pH of the hydration medium used in the preparation. It should be noted that B-ring BPD micelles remained soluble (as determined by filterability through a 0.22 micron filter) after being rehydrated in aqueous media over a pH range of 5.5 to 8.5. However, there was a tendency of the drug to self-aggregate if the pH of the rehydration medium was not kept above the pKa of the carboxyl group in the molecule.

Detail Description Paragraph:

[0117] Increasing the concentration of surfactant in aqueous solution causes a decrease in the surface tension of the solution until a certain concentration where it then becomes essentially constant with increasing concentration. The change occurs at the CMC. The most reasonable explanation of these effects is that surfactant molecule self-associates to form soluble aggregates, known as micelles. During the process of micelle formation, the hydrophobic groups form the core of the micelle and are shielded from the water to achieve a state of minimum free energy. The micelles are in dynamic equilibrium with free molecules (monomers) in solution; that is the micelles are continuously breaking down and reforming. Several physical properties change with increasing surfactant concentration above the CMC, e.g., surface tension, intensity of light scattering, osmotic pressure, equivalent conductivity, solubility of a water-insoluble solute. All of these properties could be used to determine the CMC of a surfactant. Here, we used light scattering to determine the CMC of P2K-DSPE (PEG.sub.2000-DSPE) in either distilled water or phosphate buffer.

Detail Description Paragraph:

[0128] Micelles were prepared following the procedure outlined in Example 1, except that in some of the samples, various other PEG-lipid conjugates were substituted for P2K-DSPE. The drug concentrations varied from 0.02 to 0.2 mg/ml. The thin film samples were all hydrated in an aqueous buffer at physiological pH and osmolarity using 20 mM MOPS, 5% Dextrose USP, pH. 7.0. The efficacy of the various micelle formulations in preventing self-aggregation of the PS BPD-MB (measured as A.sub.692/A.sub.720) is shown in Table 5. The presence of either dimer (A.sub.720) or monomer (A.sub.692) forms of BPD-MB in micelles was related to the degree of fatty acyl chain saturation and chain length. For example, at the lipid:drug molar ratio of 5:1, the drug incorporated into either P5K-DSPE or P5K-DPPE micelles was present as monomers, while drug dimers were present in micelles formed from either P5K-DMPE or P5K-DOPE. Drug formulated into PEG.sub.1750-steric acid micelles hydrated very rapidly although the drug was present mainly as dimers.

Detail Description Paragraph:

[0129] When loading QLT0069 into PEG-lipid micelles, the most homogeneous monomer-containing formulation was obtained when long, saturated, acyl chains were used in the micelle hydrophobic core. PEG-DSPE, with PEG molecular weights of 2000 or 5000, formed micelles with equal efficiency. Since P2K-DSPE has already been approved as an excipient in liposomal formulations (Doxil.RTM., Alza Corporation), it is a good candidate for micelles intended for clinical use.

Detail Description Paragraph:

[0131] A particularly preferred embodiment of the invention is a micelle-containing composition comprising one or more photosensitizer and one or more than one PEG-containing phospholipids which form micelles. Such compositions preferably comprise a green porphyrin photosensitizer which is preferably vertepofrinor QLT0069. The particularly preferred compositions may also comprise PEG-2000, at least distearoylphosphatidyle- thanolamine (DSPE) is said one or more than one phospholipid, or PEG.sub.2000-DSPE as said one or more than one phospholipid.

Detail Description Paragraph:

[0132] The particularly preferred compositions preferably comprise a molar ratio of lipid: photosensitizer of between about 0.5 and about 10. More preferably, the composition comprises QLT 0069 and PEG.sub.2000-DSPE, wherein the lipid: photosensitizer molar ratio ranges between about 6 and about 10. Also preferred is a composition comprising verteporfin and PEG.sub.2000-DSPE, wherein the lipid: photosensitizer molar ratio ranges between about 1 and about 6. In any particularly preferred compositions, the photosensitizer concentration is about 1-2 mg/ml and/or lyophilized.

CLAIMS:

10. A micelle-containing composition comprising QLT 0069 photosensitizer and PEG.sub.2000-DSPE, wherein the lipid : photosensitizer molar ratio ranges between about 6 and about 10.

11. A micelle-containing composition comprising veteporfin photosensitizer and PEG.sub.2000-DSPE, wherein the lipid: photosensitizer molar ratio ranges between about 2 and about 6.

13. The composition of claim 1 in a lyophilized form.

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